



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/US97/13184</p> <p>(22) International Filing Date: 28 July 1997 (28.07.97)</p> <p>(30) Priority Data: 60/022,918 1 August 1996 (01.08.96) US</p> <p>(71) Applicant (for all designated States except US): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): BYMASTER, Franklin, P. [US/US]; 8545 North 650 East, Brownsburg, IN 46112 (US). SHANNON, Harlan, E. [US/US]; 4229 Rolling Springs Drive, Carmel, IN 46033 (US).</p> <p>(74) Agents: VORNDRAN-JONES, MaCharri et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).</p>		<p>(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> Without international search report and to be republished upon receipt of that report.</p>
<p>(54) Title: METHOD FOR TREATING MENTAL RETARDATION</p>		
<p>(57) Abstract</p> <p>The present invention provides a method for treating autism and mental retardation in a mammal using a compound of Formula (I).</p> <div data-bbox="755 1113 1380 1428"><p style="text-align: right;">(I)</p></div>		

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## METHOD FOR TREATING MENTAL RETARDATION

5 This invention provides a method for using 3-(4-hexyloxy-1,2,5-thiadiazol-3-yl)-1,2,5,6-tetrahydro-1-methylpyridine, (hereinafter referred as "xanomeline"), for the treatment of autism and mental retardation.

10 Autism and mental retardation are seriously incapacitating conditions for which there has been little available treatment. The patient suffering from autism has gross and sustained impaired reciprocal social interaction. Impairment in communication is marked and sustained as well. The autistic patient suffers from restricted repetitive and  
15 stereotyped patterns of behavior, interests, and activities which are non-functional and/or abnormal in either intensity or focus. Further, the juvenile patient younger than three years old displays delays in at least one of the following areas: social interaction, language as used in social  
20 communication, or symbolic or imaginative play.

The patient suffering from mental retardation has subaverage general intellectual functioning. The onset of such subaverage intellectual functioning is before the age of 18 (eighteen) years.

25 Both mental retardation and autism can be debilitating conditions which may require institutionalization, if severe.

30 Applicants have discovered that 3-(4-hexyloxy-1,2,5-thiadiazol-3-yl)-1,2,5,6-tetrahydro-1-methylpyridine, thought to be a muscarinic agonist, can be useful for treating autism and/or mental retardation. More specifically, the invention provides a method of treating mental retardation in a mammal using 3-(4-hexyloxy-1,2,5-thiadiazol-3-yl)-1,2,5,6-tetrahydro-1-methylpyridine.  
35 Further, the present invention provides a method of treating

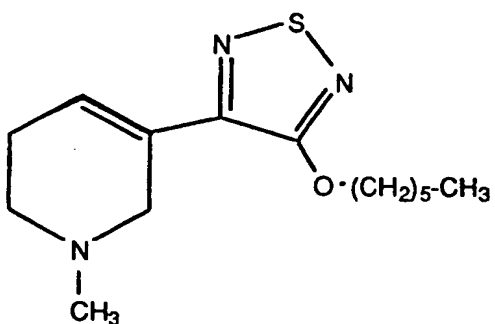
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autism in a human using 3-(4-hexyloxy-1,2,5-thiadiazol-3-yl)-1,2,5,6-tetrahydro-1-methylpyridine.

As noted hereinbefore, the compound employed in the method of the present invention is known. Methods of preparing the compound, as well as pharmaceutical formulations containing the compound, are taught by Sauerberg in U.S. Pat. No. 5,043,345 (hereinafter referred to as the "'345 patent") herein incorporated by reference. The '345 patent teaches that xanomeline can be useful for treating Alzheimer's Disease and as a stimulant of the cognitive function of the forebrain and hippocampus of mammals. Unlike Alzheimer's Disease, the onset of mental retardation is before the age of eighteen and has many different etiologies. Further, a patient suffering from autistic disorder may have average or above average intelligence in one or more skills. The autistic patient suffers from a markedly abnormal or impaired development in social interaction and communication and a markedly restricted repertoire of activity and interests. Applicants have discovered that xanomeline can be useful for the treatment of both mental retardation and/or autism. Xanomeline may address the long felt need for treatments which provide a favorable safety profile and effectively provides relief for the patient or individual suffering from autism and/or mental retardation.

The presently claimed invention provides a method for treating autistic disorder, comprising administering an effective amount of a compound of Formula I:

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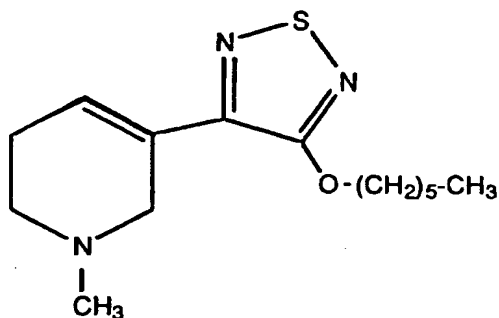
I

or

a pharmaceutically acceptable salt or solvate thereof  
to a patient in need of such treatment.

5

The presently claimed invention provides a method  
for treating mental retardation, comprising administering an  
effective amount of a compound of Formula I:



I

or

a pharmaceutically acceptable salt or solvate thereof  
to a patient in need of such treatment.

10

15

As used herein, the term "autistic disorder" shall  
refer to a condition characterized as an Autistic Disorder,  
in the DSM-IV-R. Diagnostic and Statistical Manual of  
Mental Disorders, Revised, 4th Ed. (1994) as category  
299.00. The DSM-IV-R was prepared by the Task Force on  
Nomenclature and Statistics of the American Psychiatric  
Association, and provides clear descriptions of diagnostic  
categories. The skilled artisan will recognize that there  
are alternative nomenclatures, nosologies, and  
classification systems for pathologic psychological

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conditions and that these systems evolve with medical scientific progress.

As used herein, the term "mental retardation shall refer to a condition characterized as a Mental Retardation, in the DSM-IV-R. Diagnostic and Statistical Manual of Mental Disorders, Revised, 4th Ed. (1994) as catagories 317, 318.xx, and 319. To further clarify, the present invention contemplates the treatment of mild mental retardation, moderate mental retardation, severe mental retardation, profound mental retardation, and mental retardation severity unspecified. Such mental retardation may be, but is not required to be, associated with chromosomal changes, (for example Down's Syndrome due to trisomy 21), heredity, pregnancy and perinatal problems, and other severe mental disorders.

The term "effective amount", as used herein, represents an amount of compound necessary to prevent or treat mental retardation or autistic disorder in a human susceptible to or suffering from mental retardation or autistic disorder following administration to such human. The active compound is effective over a wide dosage range. For example, dosages per day will normally fall within the range of about 0.005 to about 500 mg/kg of body weight. In the treatment of adult humans, the range of about 0.05 to about 100 mg/kg, in single or divided doses, is preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances including the condition to be treated, the choice of compound to be administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the chosen route of administration, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. While the present compound may be administered orally to humans susceptible to or suffering from mental retardation or autism, the compound is particularly well suited to be administered

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transdermally. When the compound is delivered transdermally, it is preferred that the effective amount is from about 10mg to about 100mg per day delivery of base compound. It is especially preferred that such patch  
5 delivers an effective amount for about one to seven days.

The compound may further be delivered by a variety of other pharmaceutically accepted routes including, but in no way limited to parenterally, subcutaneous, intranasal, intramuscular and intravenous routes. Such formulations may  
10 be designed to provide delayed or controlled release using formulation techniques which are known in the art.

As used herein, the term "mammal" shall refer to the Mammalia class of higher vertebrates. The term "mammal" includes, but is not limited to, a human. The term  
15 "treating" as used herein includes prophylaxis in a subject susceptible to the named condition or amelioration or elimination of the condition once it has been established.

The compounds employed in the invention are not believed to act via the GABA/benzodiazepine, serotonin, or dopamine receptor systems in humans. Rather, the activity  
20 of the present compound as a treatment for autism is believed to be based upon modulation of muscarinic cholinergic receptors. However, the mechanism by which the present compounds function is not necessarily the mechanism stated *supra.*, and the present invention is not limited by  
25 any mode of operation.

Xanomeline has been studied using accepted pharmacological methods such as oxotremorine-M verses N-methylscopolamine binding studies (Freedman et al. Br. J. Pharmacology, 93:437-445 (1988). Xanomeline inhibited the  
30 binding of  $^3\text{H}$ -oxotremorine-M with an inhibition constant ( $K_i$ ) of 2nM. The binding of the muscarinic m1 antagonist ligand,  $^3\text{H}$ -pirenzepine, to m1 receptors in hippocampus and  $^3\text{H}$ -quinuclidinyl benzilate to m2 receptors in brain stem was  
35 inhibited with  $K_i$  values of 5 and 24 nM, respectively.

Muscarinic agonists stimulate the formation of cAMP up to 10 fold in CHO m4 cells treated with pertussis

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toxin and the pharmacology is consistent with the mediation by m4 receptors. Eckols K. Soc. Neurosci Abstr., 21:2040 (1995). In this assay, xanomeline efficaciously and potently stimulated the formation of cAMP. Such studies suggest that xanomeline predominantly activates m1 and m4 receptors.

Xanomeline has a moderate affinity for 5HT<sub>2c</sub> and 5HT<sub>1D</sub> receptor subtypes as indicated by K<sub>i</sub> values of 120 and 180 nM respectively.

The clinical benefit of xanomeline for the treatment of autism can be supported by the following examples.

#### Example 1

##### Human Clinical Trials

The activity of xanomeline for treating or alleviating autism can be demonstrated by human clinical trials. The study was designed as a double-blind, parallel, placebo-controlled multicenter trial. The subjects were randomized into four groups, placebo and 25, 50, and 75 mg tid of test compound. The dosages were administered orally with food. Subjects were observed at four visits to provide baseline measurements. Visits 5-33 served as the treatment phase for the study.

During the visits, subjects are observed for behavioral, social interaction, intellectual, and concentration abilities.

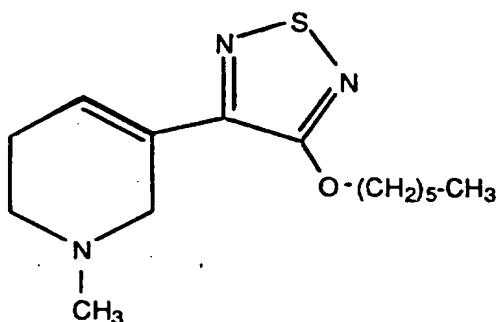
Treatment groups are compared with respect to the number and percent of subjects who ever had the symptom during the double-blind portion of the study (visits 5 through 33), at a severity that was worse than during the baseline visits (1 through 4).



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Claims

1. A method for treating autism comprising administering to a mammal in need of such treatment, an effective amount of a compound of Formula I:



or a pharmaceutically acceptable salt thereof.

2. A method of Claim 1 wherein the effective amount is from 1 mg/kg to about 100 mg/kg per day.

3. A method of Claim 2 wherein the effective amount is from about 10 mg/kg to about 100 mg/kg per day.

4. A method of Claim 1 wherein the effective amount is delivered using a transdermal patch.

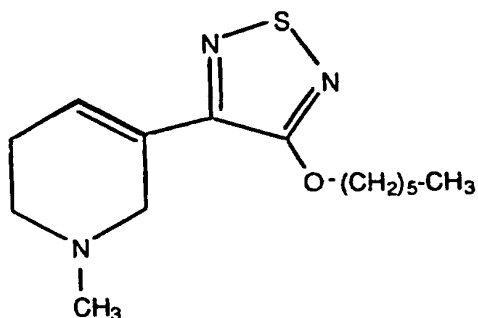
5. A method of Claim 4 wherein the transdermal patch delivers from about 10 to about 100 mg of base compound per day.

6. A method of Claim 5 wherein the transdermal patch delivers an effective amount for one (1) to seven (7) days.

7. A method of Claim 1 wherein the mammal is a human.

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8. A method for treating mental retardation comprising administering to a mammal in need of such treatment, an effective amount of a compound of Formula I:



5 or a pharmaceutically acceptable salt thereof.

9. A method of Claim 8 wherein the mammal is a human.

10. A method of Claim 9 wherein the effective amount is from 1 mg/kg to about 100 mg/kg per day.

11. A method of Claim 10 wherein the effective amount is from about 10 mg/kg to about 100 mg/kg per day.

12. A method of Claim 10 wherein the effective amount is delivered using a transdermal patch.

13. A method of Claim 12 wherein the transdermal patch delivers from about 10 to about 100 mg of base compound per day.

14. A method of Claim 13 wherein the transdermal patch delivers an effective amount for one (1) to seven (7) days.

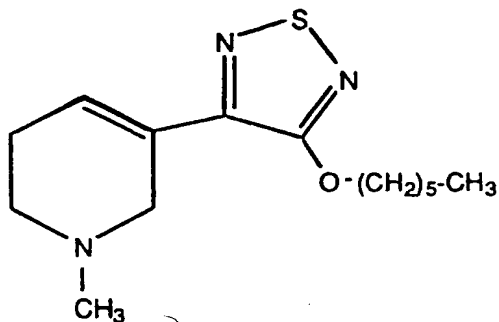
15. A method of Claim 8 wherein the mental retardation is severe mental retardation.

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16. A method of Claim 8 wherein the mental retardation is moderate mental retardation.

17. A method of Claim 8 wherein the mental retardation is mild mental retardation.

18. Use of a compound of Formula I:



or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating autism.

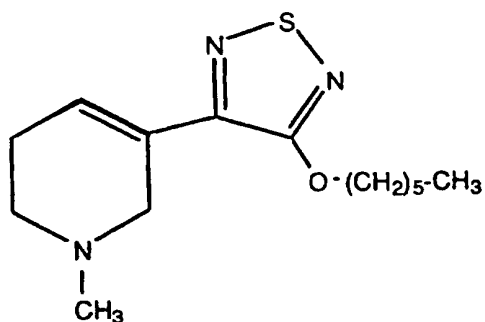
19. A use of Claim 18 wherein the compound of Formula I is delivered using a transdermal patch.

20. A use of Claim 19 wherein the transdermal patch delivers from about 10 to about 100 mg of base compound per day.

21. A use of Claim 20 wherein the transdermal patch delivers an effective amount for one (1) to seven (7) days.

22. A use of a compound of Formula I:

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or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating mental retardation.

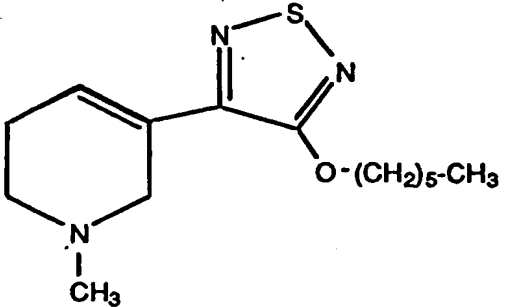
5                    23. A use of Claim 22 wherein the compound of Formula I is delivered using a transdermal patch.

10                   24. A use of Claim 23 wherein the transdermal patch delivers from about 10 to about 100 mg of base compound per day.

15                   25. A use of Claim 24 wherein the transdermal patch delivers an effective amount for one (1) to seven (7) days.



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 31/44</b>	<b>A3</b>	(11) International Publication Number: <b>WO 98/05291</b> (43) International Publication Date: 12 February 1998 (12.02.98)
<p>(21) International Application Number: PCT/US97/13184</p> <p>(22) International Filing Date: 28 July 1997 (28.07.97)</p> <p>(30) Priority Data: 60/022,918 1 August 1996 (01.08.96) US</p> <p>(71) Applicant (for all designated States except US): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): BYMASTER, Franklin, P. [US/US]; 8545 North 650 East, Brownsburg, IN 46112 (US). SHANNON, Harlan, E. [US/US]; 4229 Rolling Springs Drive, Carmel, IN 46033 (US).</p> <p>(74) Agents: VORNDRAN-JONES, MaCharri et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).</p>	<p>(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> <p>(88) Date of publication of the international search report: 14 May 1998 (14.05.98)</p>	
<p>(54) Title: METHOD FOR TREATING MENTAL RETARDATION</p> <p>(57) Abstract</p> <p>The present invention provides a method for treating autism and mental retardation in a mammal using a compound of Formula (I).</p> <div style="text-align: center;">  <p>(I)</p> </div>		

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## INTERNATIONAL SEARCH REPORT

International application No. —  
PCT/US97/13184

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/44

US CL :514/342

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — A	US 5,043,345 A (SAUERBERG et al.) 27 August 1991, see column 8, lines 25-68.	18,22 ----- 1-17, 19-21 AND 23-25

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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